

Adrenoleukodystrophy

New Approaches to a Neurodegenerative Disease

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X-LINKED ADRENOLEUKODYSTROPHY (X-ALD)¹ was first described in Germany by Siemerling and Creutzfeld in 1923.² They named it "Bronzkrankheit und Sklerosierende Encephalitis" because of the unique combination of primary adrenal insufficiency with an inflammatory demyelinating process that affects the cerebral hemispheres. In Vienna, Paul Schilder provided a detailed description of the neuropathology,³ which led to its designation as "Schilder's disease." X-linkage was proposed in 1963 on the basis of pedigree analysis.⁴ The name "adrenoleukodystrophy" was introduced 1970 by Michael Blaw and is now generally used.⁵

Until 1976, X-ALD was thought of as a poorly understood and very rare disorder that affected boys with inexorably progressive neurological and behavioral deficits that led to death within a few years. Since then, the biochemical and genetic basis of X-ALD have been defined; it occurs more frequently, the range of phenotypic expression is wider than had been recognized, and methods of prevention and therapy are emerging.

Biochemistry and Genetics

In 1976 Igarashi and colleagues⁶ made the seminal observation that saturated very long chain fatty acids (VLCFAs), such as hexacosanoic acid (C26:0), ac-

X-linked adrenoleukodystrophy (X-ALD), which was first described in 1923, was viewed until 1976 as a rare and inexorably fatal neurodegenerative disorder that affected boys. The genetic defect and biochemical abnormalities have now been defined. Ongoing research has resulted in new findings: (1) there is a wide range of phenotypic expression. At least half of patients with X-ALD are adults with somewhat milder manifestations, and women who are carriers may become symptomatic. X-ALD is often misdiagnosed as attention-deficit/hyperactivity disorder in boys and as multiple sclerosis in men and women, and is not an uncommon cause of Addison disease; (2) the incidence of X-ALD, estimated to be 1:17 000 in all ethnic groups, approximates that of phenylketonuria; (3) noninvasive and presymptomatic diagnosis and prenatal diagnosis are available; family screening and genetic counseling are key to disease prevention; and (4) new therapies, applied early, show promise. Neonatal screening is likely to become available, and a wider awareness of X-ALD and its various modes of presentation permit new proactive approaches to this distressing disorder.

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cumulate in the postmortem brain and adrenal tissue of patients with X-ALD.⁶ It was shown later that this excess is also present in plasma.⁷ The capacity to degrade VLCFA, a reaction that takes place in the peroxisome, is impaired in patients with X-ALD.¹ The defective gene in X-ALD that maps to Xq28 and codes for a peroxisomal membrane protein (ALDP) is a member of a large family of proteins referred to as the "ATP binding cassette (ABC) transporters," specifically *ABCD1*.⁸ More than 500 different mutations of *ABCD1* have been identified in patients with X-ALD (updated periodically on the X-linked Adrenoleukodystrophy Database Web site [available at: www.x-ald.nl]).

The overall frequency of X-ALD is estimated to be 1:17 000,⁹ close to that of phenylketonuria (1:14 000). All ethnic groups are affected, with no appar-

ent difference in frequency. Our laboratory has identified 1441 kindreds with 3831 affected males and 3356 women who are heterozygous for X-ALD. Markedly different phenotypes often co-occur within a family. No correlation has been demonstrated between phenotype and the *ABCD1* mutation.

Phenotypes

Until 1976, the inflammatory demyelinating process that involved the cerebral hemispheres in young and adolescent boys was the only X-ALD phenotype generally recognized. In 1976, Budka and associates¹⁰ and Griffin et al¹¹ independently and simultaneously reported a form of X-ALD that presents as

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a slowly progressive paraparesis in adults and is now referred to as "adrenomyeloneuropathy" (AMN). The pathological basis of AMN is a noninflammatory distal axonopathy that involves the long tracts of the spinal cord and, to a lesser extent, the peripheral nerves.¹² Adrenomyeloneuropathy confined to the spinal cord tracts and peripheral nerves and without radiological evidence of diffuse cerebral involvement¹³ is referred to as "pure AMN." Approximately 20% of patients with pure AMN also develop inflammatory cerebral involvement. This group is referred to as "AMN-cerebral." X-ALD can also manifest as Addison disease without evidence of neurological involvement. Such patients are referred to as the "Addison-only" phenotype.

The TABLE shows the great variability of phenotypic expression as well as the wide range of disorders for which X-ALD has been mistaken. In children and adolescents, it is often misdiagnosed as an attention-deficit/hyperactivity disorder (ADHD), and in adults as multiple sclerosis. Screening for VLCFA in at-risk relatives is identifying an increasing number of asymptomatic males with X-ALD.⁹ Women who are carriers may develop an AMN-like syndrome, but cerebral involvement and adrenal insufficiency are rare.¹⁵

Diagnosis

In the past, the diagnosis of X-ALD had often been delayed, at times until a decade or more after symptoms began or even not until after death. This is unfortunate, because therapies could have been offered, and the opportunity for timely genetic counseling was lost. Lack of awareness of X-ALD and of the wide range of the phenotypic expression of X-ALD has been the most frequent cause of delay.

The plasma VLCFA assay⁷ is the recommended diagnostic procedure in males. Plasma VLCFA levels are increased on the day of birth. The assay provides a rapid distinction between X-ALD and all other conditions it can mimic. It is particularly important that the assay be performed in all males with

idiopathic Addison disease and in men with progressive paraparesis. The early symptoms of childhood cerebral ALD are difficult to distinguish from the much more frequent ADHD. While it is not practical to screen all boys with ADHD for X-ALD, the assay should be performed when there are unusual or progressive features. It is crucially important to screen at-risk family members of known patients with X-ALD. This screen should include the extended family—hundreds of asymptomatic boys have been identified in this way.⁹

Plasma VLCFA levels are increased in women who are heterozygous for X-ALD,⁷ but false-negative test results can occur. DNA-based diagnosis in carriers is reliable¹⁶ and is recommended as the diagnostic assay in women. After the DNA mutation in an X-ALD kindred has been defined, heterozygotes can be identified accurately and rapidly by determining whether the mutation is present in at-risk women. Levels of VLCFA are increased in cultured amniocytes and chorion villus cells, which has permitted prenatal identification of hundreds of affected male fetuses,¹⁷ but confirmation by DNA analysis is recommended.

Brain magnetic resonance imaging (MRI)¹⁸ often shows characteristic, but not totally specific, changes in the cerebral forms of X-ALD. Brain MRI is often normal in patients with pure AMN and in heterozygotes.¹⁵ Spinal cord MRI in patients with AMN shows nonspecific cord atrophy, but magnetization transfer permits quantification.¹⁹

Treatment

Three modes of therapy are available at this time. They improve the prognosis of X-ALD significantly when offered in the early stages of the illness, but a definitive cure does not yet exist.

Adrenal Replacement Therapy. Adrenal hormone replacement therapy must be provided for the more than 70% of male X-ALD patients who have adrenal insufficiency. Patients with impaired adrenal reserve can be identified and treated at 6 to 12 months of age.²⁰ This can prevent a potentially life-threatening adrenal crisis, which in the

past contributed to significant morbidity and mortality, and improves general strength and well-being. However, there is currently no definitive evidence that steroid replacement therapy slows neurological progression.

Lorenzo's Oil Therapy. Lorenzo's oil is a 4:1 mixture of glyceryl-trioleate and glyceryl-trierucate, which normalizes plasma VLCFA levels in X-ALD patients within 4 weeks.²¹ While Lorenzo's oil therapy does not alter the progression after the onset of cerebral disease, recent data suggest that it may significantly reduce the risk of developing cerebral disease.²² Carefully supervised Lorenzo's oil therapy is recommended for asymptomatic boys with X-ALD who have a normal MRI result, particularly those who are younger than 8 years, and can now be provided as part of a research protocol. This must be combined with adrenal hormone replacement therapy as indicated and monitoring of brain MRI. Patients who show early evidence of cerebral involvement should be considered for hematopoietic stem cell transplantation (HSCT).²³ A placebo-controlled trial evaluating therapeutic efficacy of Lorenzo's oil in patients with pure AMN is now in progress.

Hematopoietic Stem Cell Transplantation. Hematopoietic stem cell transplantation has been shown to be of long-term benefit in the inflammatory cerebral forms of X-ALD.²⁴ Peters et al²³ have analyzed the outcome in 126 patients and found that this varied greatly with the severity of the process at the time of HSCT. An excellent outcome (92% 5-year survival) was achieved in boys in whom the involvement was still mild (performance IQ >80 and limited MRI abnormality).²³ For patients with more advanced disease, the mortality and quality of life outcomes were unfavorable and the procedure is not recommended. It is also not recommended for asymptomatic patients with normal MRI findings, because half of them may never develop the cerebral forms of X-ALD (it is not known whether HSCT benefits patients with pure AMN). The

Table. X-Linked Adrenoleukodystrophy (X-ALD) Phenotypes

Phenotypes	Total ALD, %	Symptoms/ Signs	Age at Presentation, y	Misdiagnosed as	Diagnostic Test	Follow-up Tests	Recommended Therapy
Males							
Asymptomatic (MRI normal)	Increasing	None	0 to ≥ 10	Normal	VLCFA in relatives of X-ALD patients	Monitor MRI and adrenal function; family screening	Lorenzo's oil, adrenal HRT
Asymptomatic (MRI abnormal)	Increasing	None (cognition normal)	2 to ≥ 10	Other white matter disorders	VLCFA, brain MRI	Neurological and neuropsychological testing, adrenal function	HSCT, adrenal HRT
Addison disease only (MRI normal)	20 (decreases with age)	Primary adrenocortical insufficiency, normal neurology, MRI normal	0 to ≥ 10	Other causes of Addison disease	VLCFA	Monitor MRI, neurological and neuropsychological testing	Lorenzo's oil, adrenal HRT
Addison disease only (MRI abnormal)	1	Primary adrenocortical insufficiency	0 to ≥ 10	Other causes of Addison disease	VLCFA, brain MRI	Neurological and neuropsychological testing, MRI	HSCT, adrenal HRT
Cerebral (mild) without AMN*	45	Behavior changes, school failure, dementia, audiovisual	3-10 (common) 11-21 (intermediate) ≥ 21 (rare)	ADHD, psychological disorder, Asperger syndrome, autism	VLCFA, brain MRI	Neurological and neuropsychological testing, family screening, adrenal function	HSCT, adrenal HRT
Cerebral (severe) without AMN*	2-3	Dementia, psychoses, paralysis, epilepsy, loss of vision, loss of speech, bulbar palsy	5 to adulthood	Other neurodegenerative diseases, brain tumor, psychosis, epilepsy	VLCFA, brain MRI	Adrenal function, neurological and neuropsychological testing, family screening	Adrenal HRT, general support
Pure AMN†	35	Paraparesis, sphincter disturbances, sensory changes, incoordination, pain, impotence	28 (SD,9)	Multiple sclerosis, progressive spastic paraparesis, cervical spondylosis, back injury, ALS, "triple A syndrome" ¹⁴	VLCFA	Brain MRI, adrenal function, MTS, SSEP, family screening	Adrenal HRT, possibly Lorenzo's oil,‡ physical therapy
Cerebral AMN†	15 (increases with age)	Like pure AMN plus dementia, behavioral disturbances, psychosis, epilepsy, aphasia, visual loss, bulbar palsy	28 (SD, 9)	Other causes, dementia, other neurodegenerative diseases, brain tumor, schizophrenia, Alzheimer disease, cerebrovascular disease, epilepsy, alcoholism, drug dependency	VLCFA, brain MRI	As in pure AMN plus neurological and neuropsychological testing, EEG, psychiatry, family screening	Adrenal HRT, general support, possibly HSCT§
Cerebellar	2-3	Ataxia, brainstem	Childhood; adolescence	Olivopontocerebellar degeneration	VLCFA, brain MRI	Adrenal function, neurological testing, family screening	Adrenal HRT, physical therapy
Females Heterozygous for ALD							
Asymptomatic (normal neurology)	50 (estimated) ⁹	None	Any age		DNA (VLCFA)	Neurological examination and adrenal function, monitor MRI, family screening	Genetic counseling, general support
Heterozygotes (symptoms or neurological abnormalities)	50 (estimated) ¹⁵	Paraparesis, sphincter disturbances, leg pain, sensory disturbances, incoordination, fatigue	Rare in women younger than 30 y	Multiple sclerosis, spastic paraparesis, peripheral neuropathy, cervical spondylosis, back injury, arthritis, herniated disk	DNA (VLCFA)	Adrenal function, MTS, SSEP, family screening	Genetic counseling, physical therapy, adrenal HRT, possibly Lorenzo's oil,‡ general support

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALS, amyotrophic lateral sclerosis; DNA, *ABCD1* mutation analysis; AMN, adrenomyeloneuropathy; EEG, electroencephalogram; HRT, hormone replacement therapy; HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; MTS, magnetization transfer MRI cervical cord; SSEP, somatosensory evoked potential; VLCFA, very long chain fatty acids assay in plasma.

*See Peters et al²³ for distinction between mild and severe cerebral forms.

†See text for distinction between pure and cerebral AMN.

‡Placebo-controlled trial in progress.

§HSCT being considered for mild cerebral AMN.

||False-negative test results can occur.

“window of opportunity” for HSCT is narrow. Half or more of the patients with cerebral forms who are diagnosed when they became symptomatic no longer meet the criteria for HSCT at diagnosis. Neurologically asymptomatic boys who are identified by screening at-risk relatives of known patients or those with idiopathic Addison disease have the best chance of benefiting from HSCT.

Prevention

In the absence of a definitive treatment strategy, timely identification of carriers and genetic counseling are imperative. Women heterozygous for X-ALD can be identified accurately by mutation analysis or pedigree analysis (daughters of X-ALD men are obligate heterozygotes). Studies of chorion villus sampling or amniocentesis permit

accurate prenatal identification of affected male fetuses. Preimplantation diagnosis of X-ALD is now available and offers an important new alternative for women who are carriers.

Future Directions

Unlike many other inherited metabolic disorders, X-ALD does not compromise cognitive development²⁵; hence, appropriate management improves the chances of a meaningful and productive life. This, combined with the severity of the untreated illness, the encouraging effects of therapy applied in the early stages, and its relatively high incidence,⁹ provides compelling rationale for neonatal screening. Methods to accomplish this are now under investigation and are likely to become available. New methods of therapy, such as gene therapy and new pharmacologi-

cal approaches, are being developed and some are being tested in animal models. Neonatal screening will make it possible to provide therapies to all patients before their nervous system has been damaged. Advances in therapy and prevention are taking place concurrently and will lessen the burden of this devastating disorder.

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